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ABSTRACT

Background Dyspnoea is a multidimensional experience of breathing discomfort, but its affective dimension is unfrequently assessed in people with chronic obstructive pulmonary disease (COPD). We evaluated the effectiveness of a home-based pulmonary rehabilitation (PR) programme on the physical and affective components of dyspnoea assessed by the Dyspnoea-12 (D-12) questionnaire. We also determined the baseline characteristics that contributed to the change in D-12 scores.

Methods In this retrospective study, 225 people with COPD (age, 65±11 years; forced expiratory volume in 1 s (FEV_1), 35±15% of predicted value) were enrolled into a person-centric home-based PR, consisting of a weekly supervised 90 min home session during 8 weeks. D-12 questionnaire, health status, anxiety and depressive symptoms, exercise tolerance and general fatigue were assessed at baseline (M0), at the end of PR programme (M2), and 8 (M8) and 14 months (M14) after M0. Multivariable analysis of covariance (ANCOVA) models were performed to identify the baseline characteristics that contributed to the change in D-12 scores.

Results Both physical and affective components of dyspnoea and all the other outcome measures were improved at M2, M8 and M14 compared with baseline ($p<0.05$). Baseline body mass index was the only significant independent predictor of the changes in physical dyspnoea score, while the change in the affective dimension of dyspnoea after PR was associated with FEV_1, anxiety symptoms and exercise tolerance (6 min stepper test). However, since these variables had only a small impact on the changes in D-12 questionnaire scores, results from the ANCOVA analysis should be taken cautiously.

Conclusion Both physical and affective components of dyspnoea were improved, at short term and long term, by 8 weeks of individualised home-based PR. The present results support the importance of assessing dyspnoea as a multidimensional experience during PR, warranting replication by robustly designed randomised and controlled studies.

Key messages

What is already known on this topic

- Dyspnoea is a subjective experience of breathing discomfort that contribute to inappropriate health behaviors.
- Although the effectiveness of pulmonary rehabilitation on dyspnoea has been repeatedly confirmed in COPD, its possible effects on its affective dimension is uncertain.

What this study adds

- Both physical and affective components of dyspnoea were improved by 8-week of home-based pulmonary rehabilitation at short- term and long- term.
- Body mass index was the only determinant of the change in physical domain of dyspnoea after the programme, while the severity of the airflow obstruction, anxiety symptoms and exercise tolerance contributed to the change in the affective dimension of dyspnoea.

How this study might affect research, practice or policy

- This real-life study conducted in a large sample size of people with COPD showed that beyond the physical dimension of dyspnoea, the affective one can also be improved by pulmonary rehabilitation.
- Interventions that target the anxiety distress associated to dyspnoea could be considered into pulmonary rehabilitation programme for appeasing the affective dimension of dyspnoea.

INTRODUCTION

Dyspnoea is a subjective experience of breathing discomfort,[1] observed during daily living activities in 80% of people with chronic obstructive pulmonary disease (COPD).[2] In addition to promoting a sedentary lifestyle, dyspnoea is an important contributor to fear and anxiety,[3] resulting in poor health-related quality of life[4] and inappropriate health behaviours.[5]

Dyspnoea is a multidimensional experience and recent knowledge of its pathophysiological mechanisms showed the importance of differentiating sensory (qualitative, quantitative), physical (the impact generated in daily life) and affective (anxiety, distress) domains of dyspnoea.[1] In COPD, a large battery of questionnaires can be used to evaluate dyspnoea.[6–9] In the most recent meta-analyses

reporting the effects of pulmonary rehabilitation (PR) in people with COPD,[10 11] only the sensory and physical dimensions of dyspnoea were evaluated, mainly with the Borg[6] and Visual Analogue Scales[7] for the former dimension and the Chronic Respiratory Disease Questionnaire and the modified Medical Research Council scale (mMRC)[8] for the latter dimension. This approach does not fully capture the complexity of dyspnoea by neglecting its affective dimension.[12] Multidimensional tools have been developed to address this issue, such as the Dyspnoea-12 questionnaire (D-12) or the Multidimensional Dyspnoea Profile questionnaire.[13] D-12 is a validated self-reported questionnaire including 12-item of breathlessness descriptors chosen by people with chronic respiratory diseases, that provides an evaluation of both physical and affective components of dyspnoea during daily life activities.[14]

Although the effectiveness of PR to improve the physical dimension of dyspnoea has been repeatedly confirmed in COPD,[10 11] its possible effects on its affective dimension (ie, associated with an emotional response of anxiety and/or distress) is uncertain. The focus on the affective dimension is important since the concomitant presence of anxiety and depressive symptoms and dyspnoea may lead to higher numbers of exacerbations, hospitalisations, PR withdrawals and even reduced survival.[15 16] In addition, evaluating the long-term benefits of PR on the affective component of dyspnoea has been recently determined as a research priority.[17] Furthermore, in individuals for whom the pharmacological treatment is optimal, anxiety and depressive symptoms are commonly reported as the strongest determinants of dyspnoea.[18] Other factors such as body mass index, severity of the airway obstruction, age, sex, comorbidities and physical condition had independent effects on the sensory and physical domains of dyspnoea in people with chronic respiratory diseases.[18–20] However, less is known regarding the factors associated with the affective dimensions of dyspnoea and their impact on dyspnoea changes following PR has never been reported. Targeting these factors could help for designing the most effective intervention for improving physical and affective dyspnoea in COPD.

Therefore, the aim of the study was twofold: (1) evaluate the short-term, medium-term and long-term effects of a home-based PR programme on the physical and affective components of dyspnoea assessed by the D-12 questionnaire; (2) determine the baseline characteristics that are associated to the change in affective and physical components of dyspnoea after PR. We hypothesise that, (1) both physical and affective components of dyspnoea will be improved by the home-based programme; (2) changes in physical and affective components will not be driven by the same baseline variables, supporting the importance of a multidimensional evaluation of dyspnoea.

METHODS

Study design and participants

Data from consecutive people with COPD undergoing a home-based PR programme in the North of France from September 2014 to January 2018 were retrospectively analysed. Participants were referred to the home-based PR programme by their pulmonologist who was responsible for documenting the presence of COPD according to the Global initiative for chronic obstructive lung disease classification system and validating that the participants were absent of cardiovascular contraindications to exercise training. Despite optimised pharmacological treatments, participants were referred to the programme because of symptomatic dyspnoea, exercise intolerance, difficulties in performing daily life activities or in managing the disease. Exclusion criteria were forced expiratory volume in 1 s (FEV_1) >80% of predicted value, dementia or poorly controlled psychiatric illness, neurological sequelae, or bone and joint diseases preventing physical activity. All participants signed a written informed consent prior the start of the programme.

Patient involvement

With an exception for the choice of outcomes measures, patients and their caregivers were involved in the design and conduct of the study. Since the home-based PR programme was person-centric, patients chose the physical activity, education and self-management programme according to their needs. Once the study has been published, results will be available to patients through a dedicated website (www.formactionsante.com).

Home-based PR programme

All participants received a home-based PR programme tailored to each patient's individual needs as previously described.[21 22] Briefly, the PR programme was entirely conducted at home and consisted of a weekly supervised 90 min home session, during 8 weeks. The programme started with an evaluation of the patient's needs and expectations leading to the formulation of a personalised plan. Physical training, educational, motivational and self-management plans were designed and implemented through a collaborative process between the PR team, the patient and his/her caregiver. Apart from the weekly visit of the team member who supervised the sessions during the first 8 weeks, participants were expected to perform, on their own, personalised physical training and self-management plan the rest of the week and during the 1-year follow-up period, during which there was no visit by the PR team apart from those mandated to complete the evaluation at 8 and 14 months after PR.

Education and self-management interventions were person-centric, thus, adapted to respond to individual's needs, barriers and personal goals. The centred-patients education topics covered pathophysiology of lung disease and comorbidities, medication and its use (bronchodilator, oxygen), breathing and airway clearance strategies,

prevention and recognition of exacerbations, physical exercise, stress management and emotional responses related to the disease, nutrition and weight control, smoking cessation and end-of-life planning. Emotional responses to dyspnoea were managed by behavioural therapy[16] including specific techniques such as cognitive behavioural therapy, counselling, motivational approach, cardiac coherence, mindfulness meditation and hypnosis, depending on individual's preferences or PR member training. Motivational communication was designed to implement favourable health behaviour changes, which was frequently re-evaluating and readjusting.[23] PR team members received training in the principles of behaviour change and motivational communication skills.

A cycle ergometer (Domyos essential 2, Decathlon, Villeneuve-d'Ascq, France) and/or or a stepper (Go Sport, Grenoble, France) were available at home to perform physical exercise during the 8-week training component of the programme. Cardiorespiratory training was initially performed by 10 min bouts (or sometimes shorter if the participant was unable to exercise for 10 min), at least 5 days per week, trying to achieve 30–45 min of exercise, in one or several sessions, per day. Exercise intensity was adjusted to maintain a Borg dyspnoea score between 3 and 4 on the Borg 0–10 scale. Physical training was completed with upper and lower limb muscle strengthening exercises using dumbbells, elastic and/or body weight on the same daily basis than cardiorespiratory training. Participants requiring long-term oxygen therapy performed the exercise training programme with oxygen to maintain a SpO2 >90%. They were also encouraged to increase the amount of time spend in daily life physical activities such as gardening, housekeeping, groceries. All along the intervention, PR team members emphasised the need for long-term continuation of endurance training and physical activities integrated into daily living chosen by the patient according to his/ her preferences and the local possibilities.

Data collection

Lung function, medication and comorbidity data were collected from the patient medical record provided by their pulmonologist. The burden of comorbidity was assessed using the Charlson Index.[24] Participants were evaluated at home, at the beginning (M0), at the end of 8-week PR programme (M2, short term), and at 8 months (M8, medium term) and 14 months (M14, long term) after M0, to conclude a full year of follow-up post-PR.

Dyspnoea was assessed with the French validated version of the D-12 questionnaire.[25] Each 12-item (seven for the physical and five for the affective components) score ranges from 'none' (score 0) to 'severe' (score 3) with a total score ranging from 0 to 36 (lower is better), a physical score ranging from 0 to 21 and an affective score ranging from 0 to 15. A minimal important difference (MID) of −4 to −6 points in the D-12 total score was recently reported after PR in people with severe COPD.[26] The mMRC breathlessness scale was also used to evaluate the physical dimension of dyspnoea.[8]

Health-related quality of life was evaluated with the Visual Simplified Respiratory Questionnaire (VSRQ) (eight questions on a scale from 0 to 10 with a total score ranging from 0 to 80; higher is better).[27] The Hospital Anxiety and Depression scale (14 items: seven each for anxiety and depression with minimum and maximum subscores of 0 and 21; lower is better)[28] and the Fatigue Assessment Scale (FAS) (10 items: five reflecting physical fatigue and 5 reflecting mental fatigue with a test score ranging from 10 to 50; lower is better)[29] were assessed. An anxiety or depressive symptoms score >11 indicates a probable clinical diagnosis of anxiety or depression, and an FAS score ≥22 suggests abnormal fatigue.

The 6 min stepper test (6MST) was used to evaluate exercise tolerance at home.[30] Standardised instructions were given, advising the participant to make the maximum number of steps (defined as a single complete movement of raising one foot and putting it down) possible over a 6 min period.

Statistical analyses

Statistical analyses were performed using SAS V.9.4 (SAS Institute) and statistical significance threshold was considered at 0.05. Continuous variables are expressed as mean±SD or median ±SE (IQR for non-normal distribution). Normality of distribution was assessed using histograms and Shapiro-Wilk tests. Non-normally distributed data were log-transformed before analysis. Pearson correlation were used to report the possible correlations between the physical and affective components of dyspnoea.

PR effectiveness

Linear mixed models with a random intercept to account the correlation between samples obtained within the same individuals, were used to evaluate the changes in study outcomes over time (M2, M8 and M14). Normality of the model residuals was checked for each outcome using graphs of conditional residuals. The missing data (participants who dropped-out at M2, M8 and M14) were imputed using a regression-switching approach.[31] Estimates obtained in the different imputed data sets were combined using the Rubin's rules.

Correlates of the changes in D-12 subscores and total score

Possible associations between baseline characteristics and changes in D-12 scores (physical, affective and total score) from baseline to M2, were evaluated using parametric analyses of covariance (ANCOVA), adjusted for baseline value. A significance level of 0.20 in parametric analyses was used to keep the most important explanatory variables in the final model.[32] These variables were then implemented into a backward stepwise multivariable ANCOVA model.

Characteristics of participants reaching the D-12 total score MID after PR

An additional analysis (online supplemental data) was conducted to determined factors associated with a

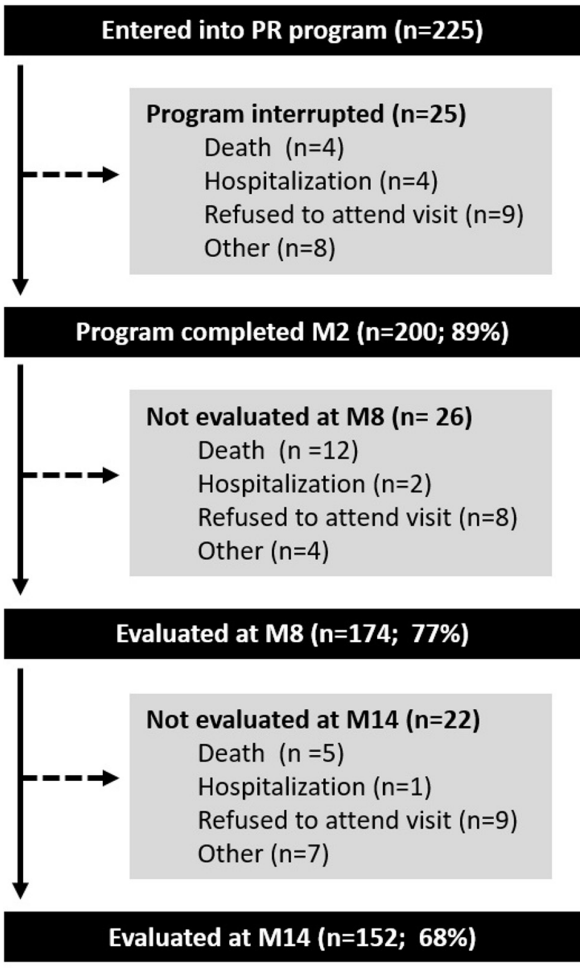

Figure 1 Flow chart of study participants. PR, pulmonary rehabilitation; M2, end of 8-week PR programme; M8, 8 months after the beginning of the intervention, M14, 14 months after the beginning of the intervention.

diminution <4 points in D-12 total score (MID reported by Beaumont *et al*[26]) after PR (M2). Participants who had reach the D-12 total score MID were defined as responders to PR. Baseline characteristics associated with responders in D-12 total score were analysed with univariate analyses using χ^2 test for categorical variables, Student's t-test for Gaussian continuous variable and Mann-Whitney U test for non-Gaussian continuous variables. To assess the independent predictors of responders, baseline characteristics associated with a p<0.20 in univariate analyses were implemented into a backward-stepwise multivariable logistic regression model using a removal criterion of p>0.05. Before developing the multivariable logistic model, we examined the log-linearity assumption for continuous characteristics using restricted cubic spline functions.

RESULTS

A total of 225 people with COPD were enrolled into the home-based programme, among them 152 (68%) participants concluded a full year of follow-up (figure 1).

Table 1 Baseline characteristics of participants

Characteristics	Total group (n=225)
Age, years	65±11
Female, nb (%)	82 (36.4)
BMI, kg/m^2	28±8
Smoking status, n (%)	
Current	36 (16.0)
Former	166 (73.8)
Never	23 (10.2)
LTOT, nb (%)	162 (72.0)
NIV, nb (%)	92 (40.9)
CPAP, nb (%)	17 (7.6)
No equipment, nb (%)	38 (16.9)
FEV_1, % of predicted	35±15
FVC, % of predicted	57±18
FEV_1/FVC, %	52±15
GOLD spirometry stages, nb (%)	
2	33 (14.7)
3	98 (43.5)
4	94 (41.8)
Charlson Index, total score	3.4±2.9

Data are presented as mean±SD or n (%).
BMI, body mass index; CPAP, continuous positive airway pressure; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; GOLD, global initiative for chronic obstructive lung disease; LTOT, long-term oxygen therapy; NIV, non-invasive ventilation.

Compared with the participants who concluded a full year of follow-up, participants who dropped out the study were characterised at baseline by a lower FEV_1, a lower affective dyspnoea score and a higher proportion of individuals requiring long term oxygen therapy. The majority of the enrolled participants were males, overweight, aged 65±11 years and had severe COPD with a mean FEV_1 of 35%±15% of predicted value (table 1). Over two-thirds of the participants used long-term oxygen therapy and 40% were on non-invasive ventilation (table 1). Among the 225 included participants, 98 (44%) and 70 (31%) patients reported an anxiety and depression subscores>11 points, respectively, and 169 (75%) had an FAS score >22 points. Strong correlations were found between the physical and affective components of dyspnoea (0.70<r < 0.80, p<0.01)

PR effectiveness

Both physical and affective components of dyspnoea and the other outcome measures were all improved at M2, M8 and M14 compared with baseline (p<0.05) (table 2). There was no significant difference between M2, M8 and M14 in any of the outcome measures. At M2, M8 and M14, 98 (49%), 88 (51%) and 81 (53%) participants, respectively, had a diminution of more than four points

Table 2 Assessments at baseline (M0) and changes in the outcomes at short term (M2), medium term (M8) and long term (M14) after PR

Assessments	M0	M2		M8		M14	
	Score	Score	ΔM2 - baseline Estimates (95% CI)	Score	ΔM8 - baseline Estimates (95% CI)	Score	ΔM14 - baseline Estimates (95% CI)
D-12 questionnaire							
Physical (0–21)	13.7±0.4	10.5±0.4	−3.1 (−4.0 to −2.3)	9.8±0.4	−3.9 (−4.9 to −3.0)	9.8±0.5	−3.8 (−4.8 to −2.9)
Affective (0–15)	8.2±0.3	6.1±0.3	−2.2 (−2.8 to −1.6)	6.0±0.4	−2.3 (−2.9 to −1.6)	5.6±0.4	−2.7 (−3.4 to −2.0)
Total score (0–36)	21.9±0.7	16.6±0.7	−5.3 (−6.7 to 4.0)	15.7±0.8	−6.2 (−7.7 to −4.7)	15.2±0.8	−6.7 (−8.3 to −5.1)
mMRC (0–4)	3.2±0.1	3.0±0.1	−0.2 (−0.4 to −0.1)	3.0±0.1	−0.3 (−0.4 to −0.1)	2.9±0.1	−0.3 (−0.5 to −0.2)
VSRQ, score (0–80)	28.9±1.4	39.0±1.4	10.1 (7.7 to 12.5)	38.2±1.5	9.3 (6.7 to 11.9)	36.4±1.5	7.5 (4.7 to 10.2)
Anxiety symptom (0–21)	9.9±0.3	8.2±0.3	−1.7 (−2.2 to −1.1)	8.0±0.3	−1.9 (−2.4 to −1.3)	7.7±0.3	−2.1 (−2.7 to −1.5)
Depressive symptom (0–21)	8.3±0.3	6.7±0.3	−1.6 (−2.1 to −1.1)	6.1±0.3	−2.3 (−2.8 to −1.7)	6.2±0.3	−2.1 (−2.7 to −1.6)
FAS, score (10–50)	28 (23 to 25)	28 (23 to 35)	−0.2 (−0.3 to −0.1)*	24 (19 to 29)	−0.2 (−0.3 to −0.1)*	24 (18 to 30)	−0.1 (−0.2 to −0.0)*
6MST, strokes	299±14	370±13	73.1 (53.7 to 92.5)	337±14	40.1 (18.1 to 62.0)	343±15	46.0 (21.7 to 70.3)

*Estimations after a log +1 transformation (FAS score was non-linear).
FAS, Fatigue Assessment Scale; mMRC, modified Medical Research Council dyspnoea scale; 6MST, 6 min stepper test; VSRQ, Visual Simplified Respiratory Questionnaire.

in D-12 total score compared with M0 (online supplemental figure S1).

Correlates of the changes in D-12 subscores and total score

Table 3 reports correlation parameters between baseline characteristics and changes in the physical, affective and total D-12 questionnaire scores, from baseline to M2. Baseline (1) body mass index (BMI) and FEV_1, (2) BMI, FEV_1, VSRQ, anxiety and depressive symptoms, fatigue and 6MST, and (3) BMI, FEV_1, VSRQ, anxiety symptoms, fatigue and 6MST, were found to be associated ($p<0.20$) with changes in (1) physical domain, (2) affective domain and (3) total score of D-12 questionnaire, respectively and were retained for the multivariate analyses. In the multivariable ANCOVA models, BMI was the only significant independent predictor of the changes in physical dyspnoea score (higher baseline BMI was associated with a decrease in physical dyspnoea score after PR). In addition to FEV_1 and 6MST, anxiety symptom was the best predictor of the changes in affective dyspnoea score (higher baseline anxiety symptoms score was associated with an increase in affective dyspnoea score after PR), while FEV_1 and 6MST were the best predictors of the change in D-12 total score (table 4).

Characteristics of participants reaching the D-12 total score MID after PR

The majority of the participants who reached the D-12 total score MID after PR (M2) were females, with higher BMI, FEV_1 and FAS score and a lower VSRQ score, compared with the participants who did not reach the MID of the D-12 total score (online supplemental table S1).

ORs of the independent predictors of responders in D-12 total score after PR are presented in online supplemental table S2.

DISCUSSION

This real-life study conducted in a large sample size of people with COPD, many of whom had chronic respiratory failure and required long-term oxygen therapy and/or non-invasive ventilation, showed that an 8 weeks of individualised and entirely home-based PR programme resulted in short-term, medium-term and long-term improvements in both physical and affective components of dyspnoea assessed by the D-12 questionnaire. To the same extent, health status, anxiety and depressive symptoms, fatigue score and exercise tolerance were also improved. An important result of this study is that, despite their strong correlation, improvements in physical and affective domains of dyspnoea after PR were not drive by the same baseline characteristics. A higher BMI was the only determinant of a reduction in physical domain of dyspnoea after PR, while the change in the affective dimension of dyspnoea after PR was associated with FEV_1, anxiety symptoms and exercise tolerance.

Table 3 Association between baseline characteristics and changes in D-12 questionnaire scores at short term (M2)

	D-12 Physical ΔM2 - baseline		D-12 Affective ΔM2 - baseline		D-12 Total ΔM2 - baseline	
Baseline	Estimates±SE	P value	Estimates±SE	P value	Estimates±SE	P value
Age, 1 year increase	0.01±0.03	0.67	0.03±0.02	0.22	0.04±0.05	0.40
Sex, female versus male	0.83±0.74	0.26	−0.07±0.56	0.90	0.79±1.19	0.51
BMI,1 kg/m^2 increase	−0.12±0.04	<0.01	−0.07±0.03	0.03	−0.19±0.06	<0.01
FEV$_1$, 1% of predicted value increase	−0.07±0.02	<0.01	−0.06±0.02	<0.001	−0.13±0.04	<0.001
Charlson Index, 1-point increase	−0.03±0.12	0.78	0.11±0.10	0.29	0.15±0.20	0.46
VSRQ, 1-point increase	−0.04±0.03	0.26	−0.06±0.03	0.03	−0.10±0.05	0.07
Anxiety symptom, score >11	0.74±0.76	0.33	2.07±0.63	0.001	2.46±1.28	0.056
Depression symptom, score >11	0.04±0.84	0.97	0.96±0.66	0.14	0.86±1.38	0.53
FAS, 1 log in total score increase	−1.15±1.13	0.31	1.39±0.85	0.10	2.57±1.88	0.17
6MST, 1 stroke increase	−0.003±0.003	0.31	−0.005±0.002	0.01	−0.008±0.004	0.08

Results of the parametric analysis of covariance, adjusted for baseline value. mMRC scales were not included in the analysis due to the collinearity with D-12 questionnaire.
BMI, body mass index; D-12, Dyspnoea-12; FAS, Fatigue Assessment Scale; FEV$_1$, forced expiratory volume in 1 s; mMRC, modified Medical Research Council; 6MST, 6 min stepper test; VSRQ, Visual Simplified Respiratory Questionnaire.

Although these results should be taken cautiously since the variables included in the ANCOVA analysis had only a poor impact on the changes in D-12 subscores and total score, they are no less informative about the factors that influence the physical and affective domains of dyspnoea after PR, and support the importance of a multidimensional evaluation of dyspnoea.

The D-12 dyspnoea questionnaire is a recent multidimensional questionnaire validated in several chronic respiratory disease including COPD.[14 33] With a mean D-12 total score of 21.9, we reported higher score compared with previous studies in people with moderate[14] and severe COPD[25] (18.0 and 14.5, respectively). The presence of chronic respiratory failure in more than 80% of this study population and, therefore, the highly sedentary lifestyle associated with,[34] could explained the higher D-12 total score.

Table 4 Multifactorial determinants of changes in D-12 questionnaire scores

Baseline	Estimates±SE	P value
ΔM2-baseline D-12 physical		
BMI,1 kg/m^2 increase	−0.12±0.04	0.003
ΔM2-baseline D-12 affective		
FEV$_1$, 1% of predicted value increase	−0.06±0.02	0.001
Anxiety symptom, score >11	1.83±0.61	0.003
6MST, 1 stroke increase	−0.005±0.002	0.007
ΔM2-baseline D-12 total score		
FEV$_1$, 1% of predicted value increase	−0.06±0.02	<0.001
6MST, 1 stroke increase	−0.004±0.002	0.048

Results from the backward stepwise multivariable ANCOVA. A significance level of 0.20 in parametric analysis (table 3) was used to keep the most important explanatory relationship variables in the final model. Multiple imputations were used and data were adjusted for baseline value.
ANCOVA, analysis of covariance; BMI, body mass index; D-12, Dyspnoea-12; FEV$_1$, forced expiratory volume in 1 s; 6MST, 6 min stepper test.

Effectiveness of PR on dyspnoea in stable people with COPD was recently documented in a systematic review.[11] Higashimoto *et al* concluded that 4–12 weeks of PR significantly improved dyspnoea whether it was measured with mMRC, Borg scale, transitional dyspnoea index or chronic respiratory questionnaire.[11] These short-term results were similar irrespective of whether PR was delivered on an outpatient basis or at home, a result supported by previous studies.[35 36] Nevertheless, the long-term effectiveness and the changes in the affective dimension of dyspnoea were not reported in these meta-analyses. This study first showed that 1 weekly individualised home PR session, combining physical exercises, education and self-management interventions, during 8-week induced short-term and long-term benefits on both physical and affective dimensions of dyspnoea, assessed by the D-12 questionnaire. Moreover, mean changes in D-12 total score of −5.3 to −6.2 and −6.7 points at M2, M8 and M14, respectively, suggested that beyond being statistically significant, the positive changes were also clinically important for the participants and persistent over time.[26] Ekström *et al*[37] recently reported a minimal clinically important difference of 1.9 (1.3–2.4) and 1.1 (0.7–1.5) for the physical and the affective components of D-12 questionnaire, respectively. However, these results were obtained without any intervention between the two measurements, limiting the comparison with the present results. The MIDs of the physical and affective components of dyspnoea after

PR still need to be determined. Moreover, although the changes in mMRC scale were significant across time, its responsiveness to PR programme was poor and not clinically relevant. The poor mMRC sensitivity to PR has already been mentioned,[38] and highlight the importance of using multidimensional tools, such as the D-12 questionnaire to assess dyspnoea in PR settings. Finally, beyond dyspnoea, health-related quality of life, anxiety and depressive symptoms and exercise tolerance were also all improved at short term, medium term and long term after the home-based PR programme.

Baseline BMI, airway obstruction, health-related quality of life, anxiety symptoms, fatigue and exercise tolerance, had an independent effect on the short improvement in D-12 total score. With an exception for the anxiety symptoms and the exercise tolerance, these results were confirmed by the analysis of participants' characteristics who responded to PR (online supplemental data). By dissociating the two dyspnoea components, we noticed that health related quality of life and anxiety and depressive symptoms seemed to have a greater impact on the change in the affective domain of dyspnoea compared with the physical one. Although the relationship between anxiety and depressive symptoms and dyspnoea in people with COPD is known,[16] the novelty of this study was to demonstrate that baseline anxiety symptom negatively affected the evolution of affective dyspnoea at the end of PR. In other words, individuals with a baseline anxiety symptom score >11 are more likely to show a smaller improvement in the affective domain of dyspnoea after PR.

Interestingly, a higher baseline BMI was a determinant of reached D-12 total score MID and reduced physical dyspnoea after PR. Since a low BMI is often associated with severe stages of the disease such as dyspnoeic emphysematous patient, the high prevalence of individuals with long term oxygen therapy and consequently the high risk of low lean body mass could explain this result. Another explanation could be that individuals with a higher BMI at baseline (and potentially a higher muscle mass) might have trained at a higher absolute training stimulus compared with individuals with a lower BMI. However, in the absence of muscle mass measurement and accurate data regarding exercise training amount, we can only speculate about this hypothesis. Nevertheless, results from the multivariate ANCOVA analysis and from the logistic regression model should be taken cautiously. Indeed, the variables included in the models have only a poor impact on the changes in D-12 questionnaire total score and subscores. For example, an increase of 40 strokes in the baseline 6MST performance (corresponding to the minimal clinically important difference[39] would be associated with an improvement of 0.16 points in the total score of D-12 questionnaire, questioning the clinical relevance of these results.

Clinical implication

The optimal PR design to reduce the affective dimension of dyspnoea remains to be determined in COPD. However, as previously mentioned, in addition to pharmacological treatments that help to manage the anxiety-distress associated to dyspnoea, interventional strategies that appease the mind should be integrate into PR programme, especially for the persistent dyspnoeic patient.[40] Recently, original interventions coupling traditional PR and behavioural therapies were designed to improve dyspnoea, and anxiety and depressive symptoms.[16] Cognitive–behavioural therapy combined with traditional PR seems to further extend the benefits on dyspnoea, anxiety and depressive symptoms and exercise capacity in people with COPD.[41] In addition to education and physical training, the present home-based programme offered cognitive behavioural therapy, cardiac coherence, mindfulness meditation and/or hypnosis, depending on individual's preferences. These latest behavioural therapy techniques, although less popular, have showed encouraging results to reduce psychological distress and dyspnoea in people with COPD.[42 43] The holistic approach, centred on the individual (and their caregiver) in their environment, according to their needs and preferences, may have contributed to the positive short- and long-term results observed in this study, warranting replicating this finding using a randomised controlled trial.

Methodological considerations

The monocentric, non-randomised nature of this study and the absence of a control group may limit the scope of the present results that should be confirmed by robustly designed randomised and controlled studies. However, data were collected systematically and consistently as an integral part of the home-based PR including a large number of participants in a real-life setting. Moreover, the intervention was conducted according to a well-defined protocol and always by the same trained team. By improving external validity and establishment in usual care, real-life studies are useful to complement the results of traditional randomised controlled trial.[44] Reporting the number of participants using anxiolytic, benzodiazepine and/or opioid for treating anxiety and depressive symptoms could have strengthen our results, as well as the number participants who exacerbated during the 8-week programme and/or during the 1-year follow-up. However, this information was not systematically report in the patient medical record. Finally, since patients' recording of their unsupervised training sessions in a physical activity diary was optional, the adherence to physical training session cannot be report. Tracking unsupervised physical training, and especially during a long-term follow-up, is a challenge for home-based PR that has yet to be addressed. However, the present results might suggest that recording adherence to each component of PR might not be necessary for maintaining long-term

benefits after PR. A robustly designed randomised study is needed to confirm this hypothesis.

CONCLUSION

Both physical and affective components of dyspnoea were improved, at short-term, medium term and long term, by 8 weeks of individualised home-based PR in people with COPD. The improvement in physical and affective domains of dyspnoea after the intervention were not driven by the same baseline characteristics, highlighting the importance of evaluating and implementing specific strategies to improve both domains of dyspnoea. The present results should be confirmed by robustly designed randomised and controlled studies.

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REFERENCES

1 Parshall MB, Schwartzstein RM, Adams L, *et al*. An official American thoracic Society statement: update on the mechanisms, assessment, and management of dyspnea. *Am J Respir Crit Care Med* 2012;185:435–52.
2 Garrod R, Bestall JC, Paul EA, *et al*. Development and validation of a standardized measure of activity of daily living in patients with severe COPD: the London chest activity of daily living scale (LCADL). *Respir Med* 2000;94:589–96.
3 Johnson MJ, Yorke J, Hansen-Flaschen J, *et al*. Breathlessness despite optimal pathophysiological treatment: on the relevance of being chronic. *Eur Respir J* 2017;50:1701297.
4 Gruenberger J-B, Vietri J, Keininger DL, *et al*. Greater dyspnea is associated with lower health-related quality of life among European patients with COPD. *Int J Chron Obstruct Pulmon Dis* 2017;12:937–44.
5 Stoeckel MC, Esser RW, Gamer M, *et al*. Brain responses during the anticipation of dyspnea. *Neural Plast* 2016;2016:1–10.
6 Borg GA. Psychophysical bases of perceived exertion. *Med Sci Sports Exerc* 1982;14:377–81.
7 Gift AG. Validation of a vertical visual analogue scale as a measure of clinical dyspnea. *Rehabil Nurs* 1989;14:323–5.
8 Bestall JC, Paul EA, Garrod R, *et al*. Usefulness of the medical Research Council (MRC) dyspnoea scale as a measure of disability in patients with chronic obstructive pulmonary disease. *Thorax* 1999;54:581–6.
9 Meek PM, Banzett R, Parsall MB, *et al*. Reliability and validity of the multidimensional dyspnea profile. *Chest* 2012;141:1546–53.
10 McCarthy B, Casey D, Devane D, *et al*. Pulmonary rehabilitation for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2015:CD003793.
11 Higashimoto Y, Ando M, Sano A, *et al*. Effect of pulmonary rehabilitation programs including lower limb endurance training on dyspnea in stable COPD: a systematic review and meta-analysis. *Respir Investig* 2020;58:355–66.
12 Hanania NA, O'Donnell DE. Activity-Related dyspnea in chronic obstructive pulmonary disease: physical and psychological consequences, unmet needs, and future directions. *Int J Chron Obstruct Pulmon Dis* 2019;14:1127–38.
13 Banzett RB, O'Donnell CR, Guilfoyle TE, *et al*. Multidimensional dyspnea profile: an instrument for clinical and laboratory research. *Eur Respir J* 2015;45:1681–91.
14 Yorke J, Moosavi SH, Shuldham C, *et al*. Quantification of dyspnoea using descriptors: development and initial testing of the Dyspnoea-12. *Thorax* 2010;65:21–6.
15 Maurer J, Rebbapragada V, Borson S, *et al*. Anxiety and depression in COPD: current understanding, unanswered questions, and research needs. *Chest* 2008;134:43S–56.
16 Yohannes AM, Junkes-Cunha M, Smith J, *et al*. Management of dyspnea and anxiety in chronic obstructive pulmonary disease: a critical review. *J Am Med Dir Assoc* 2017;18:1096.e1–1096.e17.
17 Williams MT, Lewthwaite H, Brooks D, *et al*. Chronic breathlessness explanations and research priorities: findings from an international Delphi survey. *J Pain Symptom Manage* 2020;59:310–9.
18 Garcia-Gutierrez S, Quintana JM, Unzurrunzaga A, *et al*. Predictors of change in dyspnea level in acute exacerbations of COPD. *COPD* 2016;13:303–11.
19 Díaz AA, Morales A, Díaz JC, *et al*. Ct and physiologic determinants of dyspnea and exercise capacity during the six-minute walk test in mild COPD. *Respir Med* 2013;107:570–9.
20 Ouaalaya EH, Falque L, Dupis JM, *et al*. The determinants of dyspnoea evaluated by the mMRC scale: the French Palomb cohort. *Respir Med Res* 2021;79:100803.
21 Grosbois JM, Gicquello A, Langlois C, *et al*. Long-Term evaluation of home-based pulmonary rehabilitation in patients with COPD. *Int J Chron Obstruct Pulmon Dis* 2015;10:2037–44.
22 Gephine S, Saey D, Grosbois J-M, *et al*. Home-Based pulmonary rehabilitation is effective in frail COPD patients with chronic

respiratory failure. *Chronic Obstr Pulm Dis* 2021. doi:10.15326/jcopdf.2021.0250. [Epub ahead of print: 09 11 2021].
23 Barrecheguren M, Bourbeau J. Self-Management strategies in chronic obstructive pulmonary disease: a first step toward personalized medicine. *Curr Opin Pulm Med* 2018;24:191–8.
24 Higashimoto Y, Yamagata T, Maeda K, *et al*. Influence of comorbidities on the efficacy of pulmonary rehabilitation in patients with chronic obstructive pulmonary disease. *Geriatr Gerontol Int* 2016;16:934–41.
25 Beaumont M, Couturaud F, Jego F, *et al*. Validation of the French version of the London chest activity of daily living scale and the Dyspnea-12 questionnaire. *Int J Chron Obstruct Pulmon Dis* 2018;13:1399–405.
26 Beaumont M, Le Garrec M, Péran L, *et al*. Determination of the minimal important difference for Dyspnoea-12 questionnaire in patients with COPD, after pulmonary rehabilitation. *Clin Respir J* 2021;15:413–9.
27 Perez T, Arnould B, Grosbois J-M, *et al*. Validity, reliability, and responsiveness of a new short visual simplified respiratory questionnaire (VSRQ) for health-related quality of life assessment in chronic obstructive pulmonary disease. *Int J Chron Obstruct Pulmon Dis* 2009;4:9–18.
28 Lepine JP, Godchau M, Brun P. Anxiety and depression in inpatients. *Lancet* 1985;2:1425–6.
29 Michielsen HJ, De Vries J, Van Heck GL. Psychometric qualities of a brief self-rated fatigue measure: the fatigue assessment scale. *J Psychosom Res* 2003;54:345–52.
30 Grosbois JM, Riquier C, Chehere B, *et al*. Six-minute stepper test: a valid clinical exercise tolerance test for COPD patients. *Int J Chron Obstruct Pulmon Dis* 2016;11:657–63.
31 Buuren Svan, Groothuis-Oudshoorn K. mice : Multivariate Imputation by Chained Equations in *R*. *J Stat Softw* 2011;45:1–67.
32 Hosmer D, Lemeshow S, Sturdivant R. *Applied logistic regression*. New-York: John Wiley and Sons, Incorporated, 2013.
33 Yorke J, Swigris J, Russell A-M, *et al*. Dyspnea-12 is a valid and reliable measure of breathlessness in patients with interstitial lung disease. *Chest* 2011;139:159–64.
34 Mazzarin C, Kovelis D, Biazim S, *et al*. Physical inactivity, functional status and exercise capacity in COPD patients receiving home-based oxygen therapy. *COPD* 2018;15:271–6.
35 Holland AE, Mahal A, Hill CJ, *et al*. Home-Based rehabilitation for COPD using minimal resources: a randomised, controlled equivalence trial. *Thorax* 2017;72:57–65.
36 Nolan CM, Kaliaraju D, Jones SE, *et al*. Home versus outpatient pulmonary rehabilitation in COPD: a propensity-matched cohort study. *Thorax* 2019;74:996–8.
37 Ekström M, Bornefalk H, Sköld CM, *et al*. Minimal clinically important differences for Dyspnea-12 and MDP scores are similar at 2 weeks and 6 months: follow-up of a longitudinal clinical study. *Eur Respir J* 2021;57:2002823.
38 Perez T, Burgel PR, Paillasseur J-L, *et al*. Modified medical Research Council scale vs baseline dyspnea index to evaluate dyspnea in chronic obstructive pulmonary disease. *Int J Chron Obstruct Pulmon Dis* 2015;10:1663–72.
39 Pichon R, Couturaud F, Mialon P, *et al*. Responsiveness and minimally important difference of the 6-minute Stepper test in patients with chronic obstructive pulmonary disease. *Respiration* 2016;91:367–73.
40 Similowski T. Treat the lungs, fool the brain and appease the mind: towards holistic care of patients who suffer from chronic respiratory diseases. *Eur Respir J* 2018;51:1800316.
41 Williams MT, Johnston KN, Paquet C. Cognitive behavioral therapy for people with chronic obstructive pulmonary disease: rapid review. *Int J Chron Obstruct Pulmon Dis* 2020;15:903–19.
42 Farver-Vestergaard I, O'Toole MS, O'Connor M, *et al*. Mindfulness-based cognitive therapy in COPD: a cluster randomised controlled trial. *Eur Respir J* 2018;51:1702082.
43 Anlló H, Herer B, Delignières A, *et al*. Hypnosis for the management of anxiety and dyspnea in COPD: a randomized, sham-controlled crossover trial. *Int J Chron Obstruct Pulmon Dis* 2020;15:2609–20.
44 Roche N, Anzueto A, Bosnic Anticevich S, *et al*. The importance of real-life research in respiratory medicine: manifesto of the respiratory effectiveness group: endorsed by the International primary care respiratory group and the world allergy organization. *Eur Respir J* 2019;54:1901511.